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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,435	03/20/2001	Kerstin Krieglstein	MBP-005XX	1324

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EXAMINER	
FORD, VANESSA L	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 02/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,435	KRIEGLSTEIN, KERSTIN	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,8 and 14-18* is/are pending in the application.

4a) Of the above claim(s) *1,5,6,8 and 14-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-6, 8, 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed 10/21/2005 has been entered. Applicant's amendment and response was submitted June 22, 2005. Claims 2-4, 7 and 9-13 have been cancelled. Claims 1, 5, 6, 8 , 14, 15, 17 and 18 have been amended.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejections Withdrawn

The following rejections are withdrawn:

3. a) objection of claim 6, page 3, paragraph 4 of the Final Office action.

b) objection of claim 12, page 3, paragraph 5 of the Final Office action.

c) rejection of claims 1, 5-8 and 11-18 under 35 U.S.C. 112, first paragraph , page 4, paragraph 6 of the Final Office action.

d) rejection of claims 1, 14-15 and 18 under 35 U.S.C. 102(b), pages 5-6 paragraph 7 of the Final Office action.

e) rejection of claims 1, 5-8 and 11-18 under 35 U.S.C. 103(a), pages 6-8 paragraph 8 of the Final Office action.

f) rejection of claims 1, 14-15 and 18 under 35 U.S.C. 102(b), pages 6-8 paragraph 9 of the Final Office action.

Rejections Maintained

4. The rejection of claims 1 and 14-18 under 35 U.S.C. 102(b) as anticipated by Melton et al is maintained for the reasons set forth on pages 6-7 paragraph 8 of the previous Office Action.

The rejection was on the grounds that Melton et al teach a method of inducing neuronal differentiation and preventing the death and/or degeneration of neuronal cells *in vitro* and *in vivo* (page 4). Melton et al teach that the antagonizing agents inhibit the activity of TGF-β (page 4). Melton et al teach that the antagonizing agents (i.e. follistain, a protein containing at least one follistain module and a truncated receptor for a growth factor of the TGF-β family) of the invention can bind to growth factor and sequesters the growth factor such that it cannot bind its receptors (page 4). Melton et al teach that the invention can be used to treat neurodegenerative disorders including anoxia-ischemia, Alzheimer's disease, Parkinson's disease, neuronal damage resulting from trauma and neural degeneration (page 5). Melton et al also teach that the invention can be used to treat patients with ALS (page 17). Melton et al teach that the antagonizing agents can be administered by many administration routes such as intravenous and oral administration (page 19).

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant's arguments

A) Applicant urges that Melton et al only disclose inhibition of a signal transduction by a TGF-β type growth factor (page 5, line 22). Applicant urges that the reference is silent regarding the treatment of damaged neurons by inhibiting the biological activity of TGF-β on the neurons as claim 1 requires.

B) Applicant urges that Melton et al clearly teach that TGF-β signals instruct cells towards non-neuronal facts which is the opposite of treating damaged neurons. Applicant urges that Melton et al do not anticipate the claimed invention.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed June 22, 2005 have been fully considered but they are not persuasive.

A) Melton et al teach that treatment of patients suffering from degenerative conditions can include the application of neutralizing polypeptides or agents which mimic their effects in order to manipulate apoptosis of neurons which give rise to the loss of neurons. Melton et al discloses a method for inducing neuronal differentiation and preventing the death or degeneration of neuronal cells *in vivo* by antagonizing a signalling pathway for a growth factor of the TGF-β family and pharmaceutical preparations comprising a neutralizing agent capable of antagonizing said pathway. Melton et al further teach that therapeutic applications of agents that are encompassed by the invention (e.g. activin antagonist) can be used alone or in conjunction with other neurotrophic factors to prevent or reverse motor neuron degeneration in patients

suffering from disorders such as ALS. Thus, it is the Examiner's position that the prior art reference anticipates the claimed invention.

B) To address Applicant's remarks regarding Melton et al teaching the opposite of the claimed invention, it should be noted Melton et al teach that the pharmaceutical composition of the invention can be used for the treatment of patients suffering from degenerative conditions including apoptosis of neurons which give rise to the loss of neurons. Therefore, the prior art reference anticipates the claimed invention.

5. The rejection of under 35 U.S.C. 103(a) as unpatentable over Logan et al in view of Alexandria et al and further in view of Mattson et al is maintained for claims 5-6 and 8 for the reasons set forth on pages 12-13, paragraph 11 of the previous Office

The rejection was on the grounds that Logan *(WO 93/19783)* teaches methods of for preventing, suppressing or treating a central nervous system pathology by contacting tissue with an agent (i.e. anti -TGF-β antibodies and TGF-β antagonists) that inhibits TGF-β activity (see the Abstract). Logan *(WO 93/19783)* teaches that after a penetrating injury of the brain or spinal cord (which include predamaged neurons), there is a failure of axonal growth (page 1). Logan *(WO 93/19783)* teaches that there are no therapies available to promote successful regeneration and functional reconnection of damaged neural pathways (predamaged neurons) (page 2). Logan *(WO 93/19783)* also teach that compositions containing the TGF-β inhibitors can be administered by infusion (i.e. intravenously) (Example 2). However, Logan teaches a method of administering agents including anti -TGF-β antibodies and TGF-β antagonists) to inhibit the activity of TGF-β in the central nervous system (page 3).

Logan *(WO 93/19783)* does not teach the use of compound for disintegrating blood clots.

Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Alexandria et al teach that tissue plasminogen activator is effective in lysing blood clots in animals.

Mattson et al teach that neuroprotective factors such as TGF-β are expressed in response to brain injury (see the Abstract). Mattson et al teach that within minutes

following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs (page 5).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the urokinse or tissue plasminogen activator of Alexandria et al to the pharmaceutical compositions comprising TGF-β antagonists of Logan *(WO 93/19783)* used in the method for inhibiting the biological activity of TGF on predamaged neurons in cerebral disorders because Mattson et al teach that within minutes following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs. Therefore, one of skill in the art would be motivated to add the urokinase and plasminogen activator as taught by Alexander et al because Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Additionally, Alexander et al has shown that tissue plasminogen activator is effective in lysing blood clots in animals. It would be expected barring evidence to the contrary that the addition of urokinase or tissue plasminogen activator would disintegrate blood clots because it is well known in the art that the prevention of blood clots would be necessary for treatment of central nervous systems disorders to stop cerebral hemorrhaging.

Applicant's Arugments

A) Applicant urges that claims 1 and 5 specifically require treating damaged neurons with a compound that prevents neuronal apoptosis. Applicant urges that the compounds in the prior art do not inhibition of extracellular matrix deposition in order to retard scar formation.

B) Applicant urges that patent law requires that each limitation of the claims under consideration to establish a case of *prima facie* obviousness. Applicant urges that the other references do not overcome the deficiencies of Logan et al.

Applicant urges that the rejection should be withdrawn.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed October 21, 2005 have been fully considered but they are not persuasive.

A) It should be remembered that this rejection is maintained for claims 5-8, which are drawn to a pharmaceutical composition comprising a first compound for preventing neuronal apoptosis by inhibiting the activity of TGF-β and a second compound for the disintegrating blood clots and a pharmaceutically acceptable carrier.

Logan et al teach pharmaceutical compositions comprising agents including anti - TGF-β antibodies and TGF-β antagonists) to inhibit the activity of TGF-β in the central nervous system. Logan teach that these inhibitors can be formulated with pharmaceutically acceptable carriers. Logan et al do not teach compounds for the disintegrating blood clots. However, Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage and disintegrating blood clots. One of skill in the art would be motivated to combine the two compounds into a pharmaceutical composition because Mattson et al teach that within minutes following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs. Therefore, one of skill in the art would be motivated to add the urokinase and plasminogen activator to a composition comprising TGF-β inhibitors because Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. It should be remembered that the claims are drawn to a product and a

recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

There is nothing on the record to suggest that the combination of prior art references do not teach the claimed invention.

B) To address Applicant's comments regarding establishing a case of *prima facie* obviousness, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

New Grounds of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1 and 14-18 are rejected under 35 U.S.C. 103(a) as unpatentable over Melton et al *(WO 95/10611, published April 20, 1995)* in view of Mattson et al *(Journal of Neurotrama, Volume 11, Number 1, 1994)* and in further view of Alexander et al *(Neurosurgery, 1990, 26/4, p. 559-564, (Abstract only)).*

Claims 1 and 14-18 are drawn to a method for preventing neuronal apoptosis by inhibiting the biological activity of transforming growth factor β on damaged neurons in a cerebral disorder, said method comprising providing a patient having damaged neurons caused by a cerebral disorder and treating said damaged neurons in said patient with a first compound that inhibits the biological activity of transforming growth factor β on said predamaged neurons and a pharmaceutical composition comprising a first compound that prevents neuronal apoptosis by inhibiting the biological activity of TGF-β on said damaged neurons.

Melton et al teach a method of preventing the death and/or degeneration of neuronal cells *in vitro* and *in vivo* (page 4). Melton et al teach that the antagonizing agents inhibit the activity of TGF-β (page 4). Melton et al teach that the antagonizing agents (i.e. follistain, a protein containing at least one follistain module and a truncated receptor for a growth factor of the TGF-β family) of the invention can bind to growth factor and sequesters the growth factor such that it cannot bind its receptors (page 4). Melton et al teach that the invention can be used to treat neurodegenerative disorders including anoxia-ischemia, Alzheimer's disease, Parkinson's disease, neuronal damage resulting from trauma and neural degeneration (page 5). Melton et al also teach that the invention can be used to treat patients with ALS (page 17). Melton et al teach that the

antagonizing agents can be administered by many administration routes such as intravenous and oral administration (page 19).

Melton et al teach do not teach the use of compound for disintegrating blood clots.

Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Alexandria et al teach that tissue plasminogen activator is effective in lysing blood clots in animals.

Mattson et al teach that neuroprotective factors such as TGF-β are expressed in response to brain injury (see the Abstract). Mattson et al teach that within minutes following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs (page 5).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the urokinse or tissue plasminogen activator of Alexandria et al to the pharmaceutical compositions comprising TGF-β antagonists of Melton et al used in the method for inhibiting the biological activity of TGF on damaged neurons in cerebral disorders because Mattson et al teach that within minutes following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs. Therefore, one of skill in the art would be motivated to add the urokinase and plasminogen activator as taught by Alexander et al because Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Additionally, Alexander et al has shown that tissue plasminogen activator is effective in lysing blood clots in animals. It would be

expected barring evidence to the contrary that the addition of urokinase or tissue plasminogen activator would disintegrate blood clots because it is well known in the art that the prevention of blood clots would be necessary for treatment of central nervous systems disorders to stop cerebral hemorrhaging.

7. Claims 5-6 and 8 are rejected under 35 U.S.C. 103(a) as unpatentable over Melton et al *(WO 95/10611, published April 20, 1995)* in view of Mattson et al *(Journal of Neurotrama, Volume 11, Number 1, 1994)* and in further view of Alexander et al *(Neurosurgery, 1990, 26/4, p. 559-564, (Abstract only)).*

Claims 5-6 and 8 are drawn to a pharmaceutical composition comprising a first compound for preventing neuronal apoptosis by inhibiting the biological activity of TGF-β on damaged neurons caused by a cerebral disorders and a second compound for disintegrating blood clots wherein said first and second compounds are formulated in a pharmaceutically acceptable carrier.

Melton et al teach compositions comprising antagonizing agents such as a truncated receptor for a growth factor of the TGF-β family (). Melton et al teach that compositions of invention are formulated in pharmaceutically acceptable salts or biologically acceptable medium such as water, buffered saline or polyol (pages 17-18). Melton et al teach that the compositions can be administered by a desired route of administration such as oral or intravenous (page 18).

Melton et al do not teach the use of compound for disintegrating blood clots.

Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Alexandria et al teach that tissue plasminogen activator is effective in lysing blood clots in animals.

Mattson et al teach that neuroprotective factors such as TGF-β are expressed in response to brain injury (see the Abstract). Mattson et al teach that within minutes following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs (page 5).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the urokinse or tissue plasminogen activator of Alexandria et al to the pharmaceutical compositions comprising TGF-β antagonists of Melton et al used in treatment of cerebral disorders because Mattson et al teach that within minutes following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs. Therefore, one of skill in the art would be motivated to add the urokinase and plasminogen activator as taught by Alexander et al because Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Additionally, Alexander et al has shown that tissue plasminogen activator is effective in lysing blood clots in animals. It would be expected barring evidence to the contrary that the addition of urokinase or tissue plasminogen activator would disintegrate blood clots because it is well known in the art that the prevention of blood clots would be necessary for treatment of central nervous systems disorders to stop cerebral hemorrhaging.

Conclusion

8. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
February 15, 2006

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